Claims

1. A method of inducing differentiation of mammary epithelial cells, the method comprising administering an effective amount of galanin or a functional analog or agonist thereof to the mammary epithelial cells.

2. A method of inducing differentiation of mammary epithelial cells in a mammal, the method comprising increasing the level of galanin or a functional analogor agonist thereof in the mammary tissue of the mammal.

3. A method of increasing milk production in a mammal, the method comprising increasing the level of galanin or a functional analog or agonist thereof in the mammary tissue of the mammal.

4. A method as claimed in any one of claims 1 to 3, wherein the level of galanin is increased by administering to a mammal an amount of galanin or a functional analog or agonist thereof effective to induce differentiation of mammary epithelial cells and/or increase milk production in the mammal.

5. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is a polypeptide comprising the following fragment: GWTLNSAGYLLGP (SEQ ID NO:1).

6. A method as claimed in any one of claims 1 to 4, wherein the galanin is a human galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAVGNHRSFSDKNGLTS (SEQ ID NO:2) or a functional equivalent thereof or a functional fragment thereof.

7. A method as claimed in any one of claims 1 to 4, wherein the galanin is a bovine galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHALDSHRSFQDKHGLA (SEQ ID NO:3) or a functional equivalent thereof or a functional fragment thereof.

8. A method as claimed in any one of claims 1 to 4, wherein the galanin is a porcine galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAIDNHRSFHDKYGLA (SEQ ID NO:4) or a functional equivalent thereof or a functional fragment thereof.

9. A method as claimed in any one of claims 1 to 4, wherein the galanin is a rat galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAIDNHRSFSDKHGLT (SEQ ID NO:5) or a functional equivalent thereof or a functional fragment thereof.

10. A method as claimed in any one of claims 1 to 4, wherein the galanin analog has the following amino the amino acid sequence: GWTLNSAGYLLGPHAVNHRSFSDKNGLTS (SEQ ID NO:6) or a functional equivalent thereof or a functional fragment thereof.

11. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is a human GALP (1-60) polypeptide having the following amino acid sequence: APAHRGRGGWTLNSAGYLLGPVLHLPQMGDQDGKRETALEILDLWKAIDGLP YSHPPQPS (SEQ ID NO:11) or a functional equivalent thereof or a functional fragment thereof.

12. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is a porcine GALP (1-60) polypeptide having the following amino acid sequence: APVHRGRGGWTLNSAGYLLGPVLHPPSRAEGGGKGKTALGILDLWKAIDGLP YPQSQLAS (SEQ ID NO:12) or a functional equivalent thereof or a functional fragment thereof.

13. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is a rat GALP (1-60) polypeptide having the following amino acid sequence: APAHRGRGGWTLNSAGYLLGPVLHLSSKANGGRKTDSALEILDLWKAIDGLR YSRSPRMT (SEQ ID NO:13) or a functional equivalent thereof or a functional fragment thereof.

14. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is selected from the group consisting of:

(i) Galanin–(2-29) (i.e. deletion of first amino acid);

(ii) Galanin–(3-29) (i.e. deletion of first 2 amino acids);

(iii) Galanin-(1-15) (i.e. deletion of amino acids 16-29/30);

(iv) Galanin-(1-16) (ie. deletion of amino acids 17-29/30);

(v) M40: galanin-(1-13)-Pro-Pro-Ala-Leu-Ala-Leu-Ala-amide;

(vi) M15 (galantide): Gly-Trp-Thr-Leu-Asn-Ser-Ala-Gly-Tyr-Leu-Leu-Gly-Pro-Gln-Gln- Phe-Phe-Gly-Leu-Met-NH_2 (SEQ ID NO: 13);

(vii) M35: galanin (1-13)-bradykinin (2-9) amide;

(viii) M32: galanin (1-13)-neuropeptide Y(25-36) amide; and

(ix) C7: galanin(1-13)-spantide amide.

15. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is an agonist of the GalR2 receptor.

16. A method as claimed in claim 15, wherein the agonist of the GalR2 receptor is a GALP(1-60) polypeptide or galanin(2-16).

17. A method as claimed in any one of claims 1 to 3, wherein the level of galanin in the mammary tissue is increased by administering to the mammal an amount of estrogen or a functional analog thereof effective to increase expression of galanin in the mammal. In one embodiment, the estrogen analog is estradiol.

18. A method as claimed in any one of claims 1 to 17, wherein the increase in the level of galanin or a functional analog or agonist thereof is brought about in conjunction with an increase in level or activity of prolactin or an analog thereof.

19. A method as claimed in any claim 18, wherein galanin or an analog or agonist thereof is administered to the mammal in conjunction with prolactin or an analog thereof.

20. A method as claimed in any one of claims 1 to 19, wherein the mammal is selected from the group consisting of primates including human beings, cows, sheep, goats, horses, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent or murine species.

21. A method of enhancing mammary development in a mammal, the method comprising increasing the level of galanin or a functional analog or agonist thereof and increasing the level of prolactin or an analog thereof.

22. A method as claimed in claim 21 which comprises administering galanin or an analog or agonist thereof in conjunction with prolactin or an analog thereof.

23. A method as claimed in claim 21 or claim 22, wherein the galanin analog is a polypeptide comprising the following fragment: GWTLNSAGYLLGP (SEQ ID NO:1).

24. A method as claimed in claim 21 or claim 22, wherein the galanin is a human galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAVGNHRSFSDKNGLTS (SEQ ID NO:2) or a functional equivalent thereof or a functional fragment thereof.

25. A method as claimed in claim 21 or claim 22, wherein the galanin is a bovine galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHALDSHRSFQDKHGLA (SEQ ID NO:3) or a functional equivalent thereof or a functional fragment thereof.

26. A method as claimed in claim 21 or claim 22, wherein the galanin is a porcine galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAIDNHRSFHDKYGLA (SEQ ID NO:4) or a functional equivalent thereof or a functional fragment thereof.

27. A method as claimed in claim 21 or claim 22, wherein the galanin is a rat galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAIDNHRSFSDKHGLT (SEQ ID NO:5) or a functional equivalent thereof or a functional fragment thereof.

28. A method as claimed in claim 21 or claim 22, wherein the galanin analog has the following amino the amino acid sequence: GWTLNSAGYLLGPHAVNHRSFSDKNGLTS (SEQ ID NO:6) or a functional equivalent thereof or a functional fragment thereof.

29. A method as claimed in claim 21 or claim 22, wherein the galanin analog is a human GALP (1-60) polypeptide having the following amino acid sequence: APAHRGRGGWTLNSAGYLLGPVLHLPQMGDQDGKRETALEILDLWKAIDGLP YSHPPQPS (SEQ ID NO:11) or a functional equivalent thereof or a functional fragment thereof.

30. A method as claimed in claim 21 or claim 22, wherein the galanin analog is a porcine GALP (1-60) polypeptide having the following amino acid sequence: APVHRGRGGWTLNSAGYLLGPVLHPPSRAEGGGKGKTALGILDLWKAIDGLP YPQSQLAS (SEQ ID NO:12) or a functional equivalent thereof or a functional fragment thereof.

31. A method as claimed in claim 21 or claim 22, wherein the galanin analog is a rat GALP (1-60) polypeptide having the following amino acid sequence: APAHRGRGGWTLNSAGYLLGPVLHLSSKANGGRKTDSALEILDLWKAIDGLR YSRSPRMT (SEQ ID NO:13) or a functional equivalent thereof or a functional fragment thereof.

32. A method as claimed in claim 21 or claim 22, wherein the galanin analog is selected from the group consisting of:

(i) Galanin–(2-29) (i.e. deletion of first amino acid);

(ii) Galanin–(3-29) (i.e. deletion of first 2 amino acids);

(iii) Galanin-(1-15) (i.e. deletion of amino acids 16-29/30);

(iv) Galanin-(1-16) (ie. deletion of amino acids 17-29/30);

(v) M40: galanin-(1-13)-Pro-Pro-Ala-Leu-Ala-Leu-Ala-amide;

(vi) M15 (galantide): Gly-Trp-Thr-Leu-Asn-Ser-Ala-Gly-Tyr-Leu-Leu-Gly-Pro-Gln-Gln- Phe-Phe-Gly-Leu-Met-NH_2 (SEQ ID NO: 13);

(vii) M35: galanin (1-13)-bradykinin (2-9) amide;

(viii) M32: galanin (1-13)-neuropeptide Y(25-36) amide; and

(ix) C7: galanin(1-13)-spantide amide.

33. A method as claimed in claim 21 or claim 22, wherein the galanin analog is an agonist of the GalR2 receptor.

34. A method as claimed in claim 21 or claim 22, wherein the agonist of the GalR2 receptor is a GALP(1-60) polypeptide or galanin(2-16).

35. A method as claimed in any one of claims 21 to 34, wherein the mammal is selected from the group consisting of primates including human beings, cows, sheep, goats, horses, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent or murine species.

36. A transgenic mammal having integrated in its genome a nucleic acid construct comprising a sequence encoding galanin or an analog thereof, wherein the transgenic mammal expresses galanin or an analog thereof at an elevated level compared to an equivalent non-transgenic mammal, and wherein the level of milk production is increased in the transgenic mammal when compared to an equivalent non-transgenic mammal.

37. A transgenic mammal as claimed in claim 36, wherein the transgenic mammal is a cow, sheep, pig or goat.

38. A transgenic mammal as claimed in claim 36 or claim 37, wherein the sequence encoding galanin is selected from a cDNA sequence as shown in SEQ ID NO:14 (which encodes human galanin) or a fragment thereof, SEQ ID NO:15 or a fragment thereof (which encodes bovine galanin) and SEQ ID NO:16 or a fragment thereof (which encodes porcine galanin).

39. A transgenic mammal as claimed in any one of claims 36 to 38, wherein the nucleic acid construct further comprises a mammary specific promoter operably linked to the sequence encoding galanin or an analog thereof.

40. A transgenic mammal as claimed in claim 39, wherein the mammary specific promoter is selected from the group consisting of the WAP promoter, the murine mammary tumour virus (MMTV) long terminal repeat, the neu-related lipocalin (NRL) promoter, the beta-casein promoter, the beta-lactoglobulin (BLG) promoter and the beta 1,4 galactosyltransferase promoter.

41. A method of inhibiting the growth of a mammary epithelial tumour in a subject, the method comprising administering to the subject an inhibitorially effective therapeutic amount of galanin or a functional analog or agonist thereof.

42. A method for the treatment of a mammary hyperproliferative disease in a subject, the method comprising administering to the subject an inhibitorially effective therapeutic amount of galanin or a functional analog or agonist thereof.

43. A method as claimed in claim 42, wherein the mammary hyperproliferative disease is breast cancer.

44. A method as claimed in any one of claims 41 to 43, wherein the galanin analog is a polypeptide comprising the following fragment: GWTLNSAGYLLGP (SEQ ID NO:1).

45. A method as claimed in any one of claims 41 to 43, wherein the galanin is a human galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAVGNHRSFSDKNGLTS (SEQ ID NO:2) or a functional equivalent thereof or a functional fragment thereof.

46. A method as claimed in any one of claims 41 to 43, wherein the galanin is a bovine galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHALDSHRSFQDKHGLA (SEQ ID NO:3) or a functional equivalent thereof or a functional fragment thereof.

47. A method as claimed in any one of claims 41 to 43, wherein the galanin is a porcine galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAIDNHRSFHDKYGLA (SEQ ID NO:4) or a functional equivalent thereof or a functional fragment thereof.

48. A method as claimed in any one of claims 41 to 43, wherein the galanin is a rat galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAIDNHRSFSDKHGLT (SEQ ID NO:5) or a functional equivalent thereof or a functional fragment thereof.

49. A method as claimed in any one of claims 41 to 43, wherein the galanin analog has the following amino the amino acid sequence: GWTLNSAGYLLGPHAVNHRSFSDKNGLTS (SEQ ID NO:6) or a functional equivalent thereof or a functional fragment thereof.

50. A method as claimed in any one of claims 41 to 43, wherein the galanin analog is a human GALP (1-60) polypeptide having the following amino acid sequence: APAHRGRGGWTLNSAGYLLGPVLHLPQMGDQDGKRETALEILDLWKAIDGLP YSHPPQPS (SEQ ID NO:11) or a functional equivalent thereof or a functional fragment thereof.

51. A method as claimed in any one of claims 41 to 43, wherein the galanin analog is a porcine GALP (1-60) polypeptide having the following amino acid sequence: APVHRGRGGWTLNSAGYLLGPVLHPPSRAEGGGKGKTALGILDLWKAIDGLP YPQSQLAS (SEQ ID NO:12) or a functional equivalent thereof or a functional fragment thereof.

52. A method as claimed in any one of claims 41 to 43, wherein the galanin analog is a rat GALP (1-60) polypeptide having the following amino acid sequence: APAHRGRGGWTLNSAGYLLGPVLHLSSKANGGRKTDSALEILDLWKAIDGLR YSRSPRMT (SEQ ID NO:13) or a functional equivalent thereof or a functional fragment thereof.

53. A method as claimed in any one of claims 41 to 43, wherein the galanin analog is selected from the group consisting of:

(i) Galanin–(2-29) (i.e. deletion of first amino acid);

(ii) Galanin–(3-29) (i.e. deletion of first 2 amino acids);

(iii) Galanin-(1-15) (i.e. deletion of amino acids 16-29/30);

(iv) Galanin-(1-16) (ie. deletion of amino acids 17-29/30);

(v) M40: galanin-(1-13)-Pro-Pro-Ala-Leu-Ala-Leu-Ala-amide;

(vi) M15 (galantide): Gly-Trp-Thr-Leu-Asn-Ser-Ala-Gly-Tyr-Leu-Leu-Gly-Pro-Gln-Gln- Phe-Phe-Gly-Leu-Met-NH_2 (SEQ ID NO: 13);

(vii) M35: galanin (1-13)-bradykinin (2-9) amide;

(viii) M32: galanin (1-13)-neuropeptide Y(25-36) amide; and

(ix) C7: galanin(1-13)-spantide amide.

54. A method as claimed in any one of claims 41 to 43, wherein the galanin analog is an agonist of the GalR2 receptor.

55. A method as claimed in any one of claims 41 to 43, wherein the agonist of the GalR2 receptor is a GALP(1-60) polypeptide or galanin(2-16).

56. A method as claimed in any one of claims 41 to 55, wherein the subject is selected from the group consisting of primates including human beings, cows, sheep, goats, horses, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent or murine species.

AMENDED CLAIMS

[received by the International Bureau on 30 December 2003 (30.12.03);
original claims 4 and 17 amended (2 pages)]

1. A method of inducing differentiation of mammary epithelial cells, the method comprising administering an effective amount of galanin or a functional analog or agonist thereof to the mammary epithelial cells.

2. A method of inducing differentiation of mammary epithelial cells in a mammal, the method comprising increasing the level of galanin or a functional analogor agonist thereof in the mammary tissue of the mammal.

3. A method of increasing milk production in a mammal, the method comprising increasing the level of galanin or a functional analog or agonist thereof in the mammary tissue of the mammal.

4. A method as claimed in claim 2 or claim 3, wherein the level of galanin is increased by administering to a mammal an amount of galanin or a functional analog or agonist thereof effective to induce differentiation of mammary epithelial cells and/or increase milk production in the mammal.

5. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is a polypeptide comprising the following fragment: GWTLNSAGYLLGP (SEQ ID NO:1).

6. A method as claimed in any one of claims 1 to 4, wherein the galanin is a human galanin polypeptide having the following amino acid sequence: GWTLNSAGYLLGPHAVGNHRSFSDKNGLTS (SEQ ID NO:2) or a functional equivalent thereof or a functional fragment thereof.

13. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is a rat GALP (1-60) polypeptide having the following amino acid sequence: APAHRGRGGWTLNSAGYLLGPVLHLSSKANGGRKTDSALEILDLWKAIDGLR YSRSPRMT (SEQ ID NO:13) or a functional equivalent thereof or a functional fragment thereof.

14. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is selected from the group consisting of:

(i) Galanin–(2-29) (i.e. deletion of first amino acid);

(ii) Galanin–(3-29) (i.e. deletion of first 2 amino acids);

(iii) Galanin-(1-15) (i.e. deletion of amino acids 16-29/30);

(iv) Galanin-(1-16) (ie. deletion of amino acids 17-29/30);

(v) M40: galanin-(1-13)-Pro-Pro-Ala-Leu-Ala-Leu-Ala-amide;

(vi) M15 (galantide): Gly-Trp-Thr-Leu-Asn-Ser-Ala-Gly-Tyr-Leu-Leu-Gly-Pro-Gln-Gln- Phe-Phe-Gly-Leu-Met-NH_2 (SEQ ID NO: 13);

(vii) M35: galanin (1-13)-bradykinin (2-9) amide;

(viii) M32: galanin (1-13)-neuropeptide Y(25-36) amide; and

(ix) C7: galanin(1-13)-spantide amide.

15. A method as claimed in any one of claims 1 to 4, wherein the galanin analog is an agonist of the GalR2 receptor.

16. A method as claimed in claim 15, wherein the agonist of the GalR2 receptor is a GALP(1-60) polypeptide or galanin(2-16).

17. A method as claimed in any one of claims 1 to 3, wherein the level of galanin in the mammary tissue is increased by administering to the mammal an amount of estrogen or a functional analog thereof effective to increase expression of galanin in the mammal.